PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 101024-1 WO	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/GB2004/001396	International filing date *(day/month/year)* 01.04.2004	Priority date *(day/month/year)* 05.04.2003
International Patent Classification (IPC) or national classification and IPC A61K31/00, A61K31/554, A61P1/10		
Applicant ASTRAZENECA AB		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 9 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
26.10.2004	22.06.2005
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Telephone No. +31 70 340- 4540 CIELEN, E.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/001396

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-29 as originally filed

   Claims, Numbers

   1-7 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

   * *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-7 (all partially)

because:

☒ the said international application, or the said claims Nos. 1, 4-7 (all partially), with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 1-6 (all partially) are so unclear that no meaningful opinion could be formed *(specify)*:

see separate sheet

☒ the claims, or said claims Nos. 1-6 (all partially) are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/001396

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	5-7
	No:	Claims	1-4
Inventive step (IS)	Yes:	Claims	7
	No:	Claims	1-6
Industrial applicability (IA)	Yes:	Claims	2, 3
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

III.i. Claims 1 and 4-7 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

III.ii. This application does not meet the requirements of Article 5 and 6 PCT, because claims 1-6 are not clear, nor sufficiently supported and the invention is not sufficiently disclosed by the description.

(a) Present claims 1-6 relate to compounds defined by reference to a desirable characteristic or property, namely "an IBAT inhibitor". The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to their pharmacological profile. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

(b) Moreover, present claims 1-6 relate to compounds which actually are not well-defined. The use of the definition "or a prodrug thereof" in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. The lack of clarity is such as to render a meaningful complete search impossible.

(c) Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the IBAT inhibitors specifically mentioned in claim 7, pharmaceutical compositions containing them and their use for the treatment or prophylaxis of constipation, with due regard to the general idea underlying the application.

No opinion of the International Search Authority will be given in respect of subject-matter which is not covered by the search report (Rule 66.1(e) PCT) (see also point **V.i**).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

V.i. (a) The present statement expressed as to novelty, inventive step and industrial applicability refers only to matter for which an International Search Report has been drawn up (i.e. only for the IBAT inhibitors specifically mentioned in claim 7, pharmaceutical compositions containing them and their use for the treatment or prophylaxis of constipation, with due regard to the general idea underlying the application).

(b) Claims 1 and 4-7 involve compositions or substances in a method of treatment of the human/animal body. For the assessment of claims 1 and 4-7 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

V.ii. The following documents are referred to in this communication:

D1 : US 2002/142054 A1 (FISCHER MILTON H ET AL) 3 October 2002 (2002-10-03)

D2 : GB 2 262 888 A (OCHI SHIGEO ; KIBUN SHOKUHIN KABUSHIKIKAISHA (JP)) 7 July 1993 (1993-07-07)

D3 : WO 03/022286 A (ASTRAZENECA UK LTD ; ASTRAZENECA AB (SE); BLOMBERG DAVID (SE); LEMUREL) 20 March 2003 (2003-03-20)

D4 : SCHILLER L R: "Review article: The therapy of constipation" ALIMENTARY PHARMACOLOGY AND THERAPEUTICS 2001 UNITED KINGDOM, vol. 15, no. 6, 2001, pages 749-763, XP001193738 ISSN: 0269-2813

V.iii. Article 33(2) PCT.

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-4 is not new in the sense of Article 33(2) PCT.

(a) In this respect, attention is drawn to the fact that the scope of claim 2 for which protection is sought as it is worded is regarded as a so-called "first medical use". Claims drafted in this way are only allowable if no other medical use has been earlier disclosed. Consequently, any document disclosing a medical use of a composition comprising an IBAT inhibitor will be novelty-destroying for the subject-matter of claim 2.

(b) Document D1 discloses gel-forming compositions of psyllium seed husks, which can be used for the treatment of constipation or other intestinal abnormalities or for lowering serum cholesterol levels in a patient (p. 2, par. [0024]). The psyllium seed husks prevent the re-absorption from bile acids in the blood, which effectively lower blood cholesterol levels (p. 5-6, par. [0059]; p. 6, par. [0063]). Even though the laxation-promoting effect of the composition is attributed to the increased moisture content and slippery characteristics of the stool (p. 2, par. [0026]), the compounds of D1 have inherently a bile acid reabsorption preventing effect. They therefore fit in the definition of an IBAT inhibitor or a bile acid reabsorption inhibitor (BARI). Therefore, the subject-matter of present claims 1-4 is not novel over D1.

(c) Document D2 discloses an inhibitor for absorption of digested and decomposed products of food and drink, comprising an acidic aqueous liquid containing sodium polyacrylate. The composition prevents *inter alia* fatness and constipation (p. 1, lines 5-13; p. 4, line 18 - p. 5, line 5; claim 1). The composition improves constipation and discharges bile acid out of the body. Due to the inhibition of the absorption of bile acid in the jejunum, the metabolism of fats in the body is promoted (p. 16, lines 4-26). Even though the link between the inhibition of the absorption of bile acid and the treatment of constipation is not explicitly disclosed, the composition of D2 has inherently a bile acid reabsorption inhibiting effect. It therefore fits in the definition of an IBAT inhibitor or a bile acid reabsorption inhibitor (BARI). Therefore, the subject-matter of present claims 1-4 is not novel over D2.

(d) Document D3 discloses pharmaceutical compositions containing the compounds of present claim 7 (p. 1, lines 3-11; p. 2, lines 19-26; examples 5-7, 9, 11, 14, 15, 26-30, 33). The compounds are IBATs, which are useful for the treatment of hyperlipidemic conditions. In view of point **V.iii(a)**, the subject-matter of present claim 2 is not novel over D3.

V.iv. Article 33(3) PCT.

The present application meets the criteria of Article 33(1) PCT, because the subject-matter of claim 7 involves an inventive step in the sense of Article 33(3) PCT.

(a) The subject-matter of present claim 7 may appear obvious in the light of the combination of D4 and D3 for the following reasons:

(1) Document D4 discloses that bile acid is a stimulant laxative used for the therapy of constipation (Table 2). It is mentioned that if enough bile acid is administered, the normal ileal absorptive capacity may be overwhelmed and sufficient bile acid may reach the colon to stimulate secretion (p. 755, left-hand column, par. 1).

The subject-matter of present claim 7 differs herefrom in that alternative compounds, namely benzothiadiazepine IBATs are used instead of bile acid, for providing sufficient bile acid in the colon to stimulate secretion.

The problem to be solved by the present application may therefore be regarded as the provision of alternative means for providing sufficient bile acid in the colon to stimulate secretion in the treatment and/or prophylaxis of constipation.

Document D3 discloses that the compounds of present claim 7 are IBATs, which are useful for the treatment of hyperlipidemic conditions (see point **V.iii(d)**). On p. 39, lines 19-27, it is mentioned that they may cause excess of bile acids in the colon due to the inhibition of the ileal bile acid transport system. It is also mentioned that an excess of bile acids in the visceral contents may provoke diarrhea [in patients not suffering from constipation].

It was therefore obvious for the person skilled in the art, knowing from D4 that an increased concentration of bile acids in the colon stimulates secretion in the treatment of constipation, and from D3 that benzothiadiazepine IBAT inhibitors may cause an excess of bile acids in the colon, to at least try to use the benzothiadiazepine IBAT inhibitors of D3 for the prevention or treatment of constipation with a reasonable expectation of success.

(2) However, in the present application, it is demonstrated that several of the benzothiadiazepines of present claim 7 can reverse constipation in the Buenos constipated dog model (description, p. 27, line 1 - p. 28, line 9).

Even if this finding was not surprising in the light of the combined teachings of D4 and D3, the Applicant states that the IBAT inhibitors of the present application have an advantage over bile acid itself, namely the present IBAT inhibitors have reduced side-effects, such as reduced absorption of nutrients, over bile acid itself (p. 3, lines 15-21). This finding was unexpected in the light of the prior art. Therefore, the subject-matter of present claim 7 involves an inventive step in the sense of Article 33(3) PCT.

(b) Dependent claims 5-6 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty and/or inventive step (Article 33(2) and (3) PCT). However, in combination with claim 7, the subject-matter of claims 5-6 would meet the requirements of the PCT in respect of novelty and/or inventive step (Article 33(2) and (3) PCT).